DETAILED ACTION

Claims 1,2,4-23 and 25 are currently pending in the instant application. Applicants have cancelled claims 3 and 24 in an amendment filed on March 6, 2008.

I. *Response to Arguments*

Applicant's arguments, filed March 6, 2008 with respect to the rejection of claims 1-9, 24 and 25 under 35 USC 112, first paragraph as failing to comply with the enablement requirement have been fully considered and are partially persuasive. The objection of claim 24 has been withdrawn.

The Examiner acknowledges that Group II was elected by Applicants and the mention of Group I was in error.

Applicants traverse the rejection of claims 1-9, 24 and 25 under 35 USC 112, first paragraph as failing to comply with the enablement requirement. Applicants have amended claim 1 to recite specific diseases given at page 71, lines 3-16 of the specification. Applicants further state that the specification is fully enabling for the presently claimed diseases. Applicants have submitted 10 references that support Applicants instant invention are capable of treating the claimed diseases.

The Examiner agrees that Applicants are enabled for the treatment of pollakiuria and urinary incontinence because of the support present in the specification. The Examiner acknowledges and has considered the 10 references submitted by Applicants. For example, the reference (exhibit 4) that discusses hypertension further states that "another study reported that intravenous administration of NS 004 reduced

mean arterial blood pressure but no effect on blood pressure was observed. It was concluded that the cardiovascular effects of NS 004 could be ascribed to the blockade of calcium channels, rather than the opening of BK channels". A lot of the references did not provide definitive support that BK channel activators can be used for the treatment of hypertension, premature birth, irritable bowel syndrome, cerebral infarction, subarachnoid hemorrhage, cerebral vasospasm, cerebral hypoxia, peripheral blood vessel disorder, anxiety, male pattern baldness, erectile dysfunction, other diabetic complication, sterility, urolithiasis and pain accompanied thereby, nocturnal enuresis, asthma, chronic obstructive pulmonary disease, cough accompanied by asthma or chronic obstructive pulmonary disease, cerebral apoplexy or traumatic encephalopathy. The Examiner wants to emphasize that providing references that state that a pathway "may be" useful in treating a disease is not adequate support for actually treating the specific disease.

Therefore, the Examiner agrees that Applicants are enabled for the treatment of chronic heart failure, angina, cardiac infarction and cerebral ischemia. However, the 10 references have not provided adequate support for the treatment of hypertension, premature birth, irritable bowel syndrome, cerebral infarction, subarachnoid hemorrhage, cerebral vasospasm, cerebral hypoxia, peripheral blood vessel disorder, anxiety, male pattern baldness, erectile dysfunction, other diabetic complication, sterility, urolithiasis and pain accompanied thereby, nocturnal enuresis, asthma, chronic obstructive pulmonary disease, cough accompanied by asthma or chronic obstructive pulmonary disease, cerebral apoplexy or traumatic encephalopathy. Therefore, the

specification is not enabled for the latter diseases. The specification is not enabling for the prophylaxis of the any of the diseases claimed in claim 1. Applicants are suggested to amend the method claims to read on the diseases that the Examiner has stated are enabled by the specification. The rejection of claims 1,2, 4-9 and 25 has been partially maintained.

II. *Information Disclosure Statement*

The information disclosure statement (IDS) submitted on March 6, 2008 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

III. *Rejection(s)*

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-9 and 25 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for a method for treatment of chronic heart failure, angina, cardiac infarction, cerebral infarction, pollakiuria, urinary incontinence and cerebral ischemia does not reasonably provide enablement for a method for treatment of hypertension, premature birth, irritable bowel syndrome,

cerebral infarction, subarachnoid hemorrhage, cerebral vasospasm, cerebral hypoxia, peripheral blood vessel disorder, anxiety, male pattern baldness, erectile dysfunction, other diabetic complication, sterility, urolithiasis and pain accompanied thereby, nocturnal enuresis, asthma, chronic obstructive pulmonary disease, cough accompanied by asthma or chronic obstructive pulmonary disease, cerebral apoplexy or traumatic encephalopathy. The specification does not provide enablement for a method for prophylaxis of any of the claimed diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case

The nature of the invention

The nature of the invention is a method for treatment of chronic heart failure, angina, cardiac infarction, cerebral infarction, pollakiuria, urinary incontinence or cerebral ischemia. Support for the intended use is found on pages 67-70 such as the relaxation effect on potassium-induced contraction of isolated rabbit urinary bladder and inhibitory effect on the rhythmic bladder contractions induced by substance P in rats.

The state of the prior art and the predictability or lack there of in the art

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of any condition mediated by a large conductance calcium-activated K channel opening activity, whether or not the condition is effected by the activity would make a difference.

Applicants are claiming a method for prophylaxis or treatment of a disease against which a large conductance calcium-activated K channel opening activity is efficacious.

Applicants' claims are therefore are drawn to a method for prophylaxis or treatment of a disease such as hypertension, irritable bowel syndrome, anxiety, erectile dysfunction, etc.

For example, Applicants are also claiming the treatment or prophylaxis of Irritable bowel syndrome. Irritable bowel syndrome (IBS) is a common problem with the intestines. It is when the intestines squeeze too hard or not hard enough and cause food to move too quickly or too slowly through the intestines. There is no cure for IBS, but medicine can help to manage or lessen your symptoms. Common symptoms include bloating and gas, mucus in the stool, constipation, abdominal pain, diarrhea, etc. Antispasmodic medicines may be prescribed to reduce cramping if your main symptom is pain. When diarrhea is a frequent problem, anti-diarrhea medicine such as loperamide may help. Therefore, treatment of irritable bowel syndrome is based upon what symptoms the patient in need has.
(<URL:http://family>doctor.org/online/famocen/home/common/digestive/disorders/112.html >)

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is minimal. The specification only gives a list of conditions mediated by the opening of a large conductance calcium-activated K channel. There are only a few working examples present for the treatment of urinary incontinence.

Test assays and procedure are provided in the specification at pages 67-70 such as the relaxation effect on potassium-induced contraction of isolated rabbit urinary bladder and inhibitory effect on the rhythmic bladder contractions induced by substance P in rats. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The breadth of the claims

The breadth of the claims is a method for prophylaxis or treatment of hypertension, premature birth, irritable bowel syndrome, cerebral infarction, subarachnoid hemorrhage, cerebral vasospasm, cerebral hypoxia, peripheral blood vessel disorder, anxiety, male pattern baldness, erectile dysfunction, other diabetic complication, sterility, urolithiasis and pain accompanied thereby, nocturnal enuresis, asthma, chronic obstructive pulmonary disease, cough accompanied by asthma or

chronic obstructive pulmonary disease, cerebral apoplexy chronic heart failure, angina, cardiac infarction, cerebral infarction, pollakiuria, urinary incontinence, cerebral ischemia or traumatic encephalopathy.

The quantity of experimentation needed and the level of the skill in the art

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases would be benefited by the effects of the opening of a large conductance calcium-activated K channel and would furthermore then have to determine which of the claimed compounds in the instant invention would provide treatment of the diseases.

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* or *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed

above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome, for example, by amending the broad method claims.

IV. *Conclusion*

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shawquia Young whose telephone number is 571-272-9043. The examiner can normally be reached on 7:00 AM-3:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shawquia Young/

Examiner, Art Unit 1626

/Kamal A Saeed, Ph.D./

Primary Examiner, Art Unit 1626